PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
P26152PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/050736	18.05.2004	19.05.2003

International Patent Classification (IPC) or national classification and IPC
A61L31/04

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.02.2005	19.09.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/050736

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-18	as originally filed
Claims, Numbers	
1-29	received on 15.02.2005 with letter of 15.02.2005
Drawings, Sheets	
1-3	as originally filed
Drawings, Figures	
1-3	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-29
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25 : due to medical treatment by surgery, there is no opinion concerning industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 25 : due to medical treatment by surgery, there is no opinion concerning industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4,6-11,14-17,20-24,27
	No:	Claims	1,5,12,13,18,19,25,26,28,29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-24,26-29
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I.

Basis of the opinion

This report has been established as if some of the amendments had not been made, since they have been considered to go beyond the disclosure as originally filed. (Rule 70.(c) PCT)

The following amendments have been made (Article 34(2)b) PCT):

Claim 1-29:

- "...demineralized bone (DMB), and a...[...] biocompatible biopolymer] carrier for the DMB [...] DMB and the biopolymer carrier both [...]"
- deletion of the method step : "annealing the resulting product in the absence of oxygen at a temperature of from 40°C to 120°C to render"

There is no support in the description as originally filed for these amendments in the newly filed set of claims.

As originally filed the object of the present invention is to provide a method for the preparation of an osteoinductive agent, the use and a kit comprising said osteoinductive agent.

The solution proposed by the applicant in the description as well in the claims as originally filed based on the method steps of modifying a naturally occurring biocompatible biopolymer [...].by subjecting the biopolymer to a source of ionizing radiation in the presence of a mediating gas and in the absence of oxygen at a temperature of from 40 °C to 120°C [...].

The natural occurring biocompatilble biopolymer may be selected from the group consisting of collagen; hyaluronic acid; demineralized bone (DMB); and mixtures thereof. (see also claim 2)

The disclosure of the invention does not refer to a biopolymer as the carrier for the DMB. Claim 2 suggests the idea that the "naturally occurring biocompatible biopolymer" selected from the group consisting of collagen, hyaluronic acid and DMB are meant equal, they are all representing a solution for the "naturally occurring biocompatible biopolymer".

It is neither form the claims as originally filed nor from the description disclosed, that DMB is not used as the "naturally occurring biocompatible biopolymer" nor that collagen or hyaluronic acid are used as **carrier for the DMB**.

The deletion of the above mentioned method step as originally claimed is not allowable, because the resulting scope of the protection is broader than as originally claimed.

For the deletion is no support present.

Re Item III_

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 25 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

- "**dispensing** the putty into a bone reconstruction site; and **closing** the site to allow bone reconstruction to take place."

For the assessment of the present claim 25 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

1 The following documents have been referred to in this communication:
D1 : US 2002/107299 A1 (SUN DEH-CHUAN ET AL) 8 August 2002 (2002-08-08)
D2: EP-A-1 270 660 (BMG INC) 2 January 2003 (2003-01-02)

2 INDEPENDENT CLAIMS 1, 13, 25, 27

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,5,12,13,18,19,25,26,28,29 is not new in the sense of Article

33(2) PCT.

2.1
Document D1 discloses a non-oxidizing polymeric medical implant. In the process of D1, a polymeric orthopaedic implant component is radiated without oxidants, such as oxygen or moisture. The finished polymeric orthopaedic component is then sealed in an oxidant-free atmosphere. This oxidant-free atmosphere is maintained during radiation. The irradiated, heat treated plastic component is then ready for use. The oxidation resistance to any oxidising agent is similar to that of the unirradiated virgin polymer. (see paragr.16-18)
It is the object of the invention of D1 to provide a method for manufacturing such an implant from the resin powder. The method for producing a polymeric medical implant includes the steps of placing the polymeric resin in a sealed container and removing a substantial portion of the oxygen from the container and repressurized with an inert gas like nitrogen or argon. The finished part in then sealed into an oxidant-free (atmosphere, see paragr. 29) package to prevent oxygen and moisture from entering.
In general, the implant is heated at a temperature of 37-70 °C. (see paragr. 19-21)
The inert gas, such as nitrogen, is flushed into the container, holding the polymer resin powder. It is important to maintain the inert gas atmosphere during the forming process to minimize oxidation. Any free radicals generated should be eliminated as soon as the forming process is completed by annealing. (see paragr. 24-26)
The disclosure of D1 is novelty destroying for the subject-matter of claims 1,5,12,13,18,19,25,26,28,29. (see Article 33 (1) and (2) PCT)

3 DEPENDENT CLAIMS 2-12,14-24,26,28,29
Dependent claims 2-12,14-24,26,28,29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

3.1
D1 has been considered as representing the most relevant prior art. (disclosure, see above)

3.2

D2 (EP 1270660 A) discloses medical materials subjected to irradiation. The medical materials of bio-absorbable and decomposed polymer include polymers selecting from collagen, hyaluronic acid, etc... and their blends. (see paragr. 18,19,21)

Based on irradiation for sterilization and cross-linking between polymer chains at final producing stage after molding in products of industrial uses, achieved by irradiation of 10 to 50 kGy. (see paragr. 25,27 and 28)
The irradiation takes place under inert gas atmosphere, such as under nitrogen or argon.
Concerning the special technical features disclosed in D2 in combination with the disclosure of D1 attack the inventive step idea of the subject-matter in claims 2-12,14-24,26,28,29.

The alleged technical features of the remaining claims 6-11,20-23,27 provide only optional design, such as a container in form of a syringe and its further limiting constructive extra-features.
Therefore the subject-matter of dependent claims 2-12,14-24,26,28,29 has been considered not involving an inventive step. (see Article 33(1) and (3) PCT)

CLAIMS

1. A method for the preparation of an osteoinductive agent including the steps of modifying demineralised bone (DMB), and a naturally occurring biocompatible biopolymer carrier for the DMB, by subjecting the DMB and the biopolymer carrier, both in the solid or dry state, either separately or in a mixture, to a source of ionising radiation in the presence of a cross-linking enhancing unsaturated mediating gas, to obtain cross-linked products; rendering the products in dry particulate form; thereafter removing any residual mediating gas; mixing the products if they are not already mixed; and disposing the products in a hermetically sealed container containing oxygen-free gas.

2. A method according to claim 1 wherein the naturally occuring biocompatible biopolymer carrier is selected from the group consisting of collagen; and hyaloronic acid; and mixtures thereof.

3. A method according to claim 1 or claim 2 wherein the said cross-linking enhancing unsaturated mediating gas is selected from the group consisting of acetylene, ethylene, and propylene.

4. A method according to any one of claims 1 to 3 wherein the step of subjecting the DMB and the biocompatible biopolymer carrier to cross-

linking ionising radiation in the presence of the mediating gas includes the step of subjecting the DMB and the biocompatible biopolymer carrier to a minimum absorbed irradiation dose of between 2 and 25 kGy.

5. A method according to any one of the preceding claims wherein the hermetically sealed container is a secondary container and wherein the method includes the further step of disposing the product inside a first primary container, which is disposed inside the hermetically sealed secondary container, the first primary container being in the form of a syringe - type container, having a plunger for dispensing the contents thereof, and an outlet opening having a diameter larger than 0.6 mm, to allow for the dispensing of the said products in a relatively viscous form, the arrangement being such that the DMB and the biocompatible biopolymer carrier are subjected to cross-linking ionising radiation whilst being disposed in the first primary container.

6. A method according to claim 5 including the further step of filling the space in the first primary container, not occupied by the products, with the said oxygen-free gas.

7. A method according to claim 5 or 6 which includes the further steps of providing a second primary container; disposing liquid in the second

primary container; and disposing the second primary container inside the hermetically sealed secondary container.

8. A method according to claim 7 including the further step of providing the said liquid in the form of pyrogen-free water.

9. A method according to any one of claims 5 to 8 which includes the further steps of disposing the hermetically sealed secondary container inside a hermetically sealed tertiary container; filling the tertiary container with oxygen-free gas; and capturing the oxygen-free gas inside the hermetically sealed tertiary container.

10. A method according to claim 9 wherein the steps of providing the secondary and tertiary containers include the step of forming these containers from a radiation stable, gas - impermeable material; and wherein the method includes the further step of subjecting the said containers and their contents, in kit form; to a terminal radiation sterilisation process, by subjecting the containers and their contents to a minimum absorbed irradiation dose of 25 kGy.

11. A method according to any one of the preceding claims which includes the further step of mixing the said products in dry particulate form with a

sterile liquid to hydrate the products to form an osteoinductive agent in the form of a pliable viscous putty.

12. A method according to claim 11 which includes the further step of dispensing the osteoinductive agent from the first primary container to a bone reconstruction site.

13. A kit for preparing and dispensing an osteoinductive agent including a modified DMB and modified naturally occurring biocompatible biopolymer carrier for the DMB, which were subjected, in the solid or dry state, to a source of ionising radiation in the presence of a cross-linking enhancing unsaturated mediating gas; and rendered in a dry particulate product, the product being disposed in a hermetically sealed container containing oxygen-free gas.

14. A kit according to claim 13 wherein the naturally occurring biocompatible biopolymer carrier is selected from the group consisting of collagen; and hyaloronic acid; and mixtures thereof.

15. A kit according to claim 13 or 14 wherein the biocompatible biopolymer carrier and the DMB are subjected in the presence of the said mediating gas to the said source of ionising radiation separately from each other and thereafter mixed.

16. A kit according to claim 13 or 14 wherein the biocompatible biopolymer carrier and the DMB are first mixed and thereafter subjected to the said source of ionising radiation in the presence of the said mediating gas.

17. A kit according to any one of claims 13 to 16 wherein the DMB and biocompatible biopolymer carrier are subjected to a minimum absorbed irradiation dose of between 2 and 25 kGy.

18. A kit according to any one of claims 13 to 17 wherein the sealed container is a secondary container and wherein the product is disposed inside a first primary container, which is disposed inside the sealed secondary container, the first primary container being in the form of a syringe - type container, having a plunger for dispensing the contents thereof and an outlet opening having a diameter larger than 0.6 mm, to allow for the dispensing of the product in a relatively viscous form, the arrangement being such that the DMB and the biocompatible biopolymer carrier are subjected to cross-linking ionising radiation whilst being disposed in the first primary container.

19. A kit according to claim 18 wherein the space in the primary container not occupied by the product is filled with the said oxygen-free gas.

20. A kit according to any one of claims 13 to 19 which includes a second primary container containing a liquid and being disposed inside the hermetically sealed secondary container.

21. A kit according to claim 20 wherein the liquid is in the form of pyrogen-free water.

22. A kit according to claim 20 or 21 wherein the hermetically sealed secondary container is disposed inside a hermetically sealed tertiary container and wherein the tertiary container is filled with oxygen-free gas.

23. A kit according to claim 22 wherein the secondary and tertiary containers are formed from a radiation stable, gas - impermeable material and are subjected, in kit form, to a terminal radiation sterilisation process.

24. A kit according to any one of claims 13 to 23 wherein the said cross-linking enhancing unsaturated mediating gas is selected from the group consisting of acetylene, ethylene and propylene.

25. A method of reconstructive bone surgery in humans or animals including the steps of providing the kit according to claim 22; opening the

secondary and tertiary containers; hydrating the dry particulate product by injecting the sterile liquid into the first primary container and mixing the liquid and the product to form a putty; dispensing the putty into a bone reconstruction site; and closing the site to allow bone reconstruction to take place.

26. An osteoinductive agent prepared in accordance with any one of claims 1 to 12.

27. An osteoinductive prepared in accordance with any one of claims 1 to 12 for use in a method of reconstructive surgery in humans or animals.

28. A method for the preparation of an osteoinductive agent substantially as herein described with reference to the accompanying drawings.

29. A kit for preparing and dispensing an osteoinductive agent substantially as herein described and as illustrated in the accompanying drawings.